Message

From: Schweer, Greg [Schweer.Greg@epa.gov]
Sent: 5/19/2018 2:17:36 AM
To: Allison, Rose [Allison.Rose@epa.gov]; Bauer, Jeff [Bauer.Jeff@epa.gov]
CC: Alwood, Jim [Alwood.Jim@epa.gov]; Camacho, Iris [Camacho.Iris@epa.gov]; Irwin, William [Irwin.William@epa.gov]; Vendinello, Lynn [Vendinello.Lynn@epa.gov]
Subject: Fwd: Request Suspend P-18-0101 for further review
Attachments: RE: Sustainable Futures TME/PMN Needs Your Attention; ATT00001.htm; Category_Polyol_Esters_September_2010.pdf; ATT00002.htm

Jeff and Rose,

I expect that Jeff M. and/or Nancy will call about this on Monday when I am out. I am not certain if Jeff Bauer is on compressed on Monday.

So, I have taken the liberty of cc'ing Iris and William on this email.

Sent from my iPhone

Begin forwarded message:

> **From:** Anastasia Coots <Anastasia_Coots@cargill.com>
> **Date:** May 18, 2018 at 9:46:30 PM EDT
> **To:** "Beck, Nancy" <Beck.Nancy@epa.gov>, "Bauer, Jeff" <Bauer.Jeff@epa.gov>, "Morris, Jeff" <Morris.Jeff@epa.gov>
> **Cc:** Robin Eichen-conn <Robin_Eichen-Conn@cargill.com>, "Hanley, Mary" <Hanley.Mary@epa.gov>, "Bolen, Derrick" <bolen.derrick@epa.gov>, "schweer.greg@epa.gov" <schweer.greg@epa.gov>, Brent Aufdembrink <Brent_Aufdembrink@cargill.com>
> **Subject: FW: Request Suspend P-18-0101 for further review**
>
> Thanks Nancy,
>
> My apology for my delay on our response. We have had a few phone calls where we are getting closer to an understanding but we still have concerns. Our understanding is that we should be able to eliminate the risk assessors concerns with new OECD 422 testing of the PMN substance. There are definitely still some questions around the testing that are not clear but these details were passed through the risk assessor to the PM and we haven't seen them in writing so it might just be my misunderstanding.
>
> Cargill would like EPA management to provide sign-off on the agreement that we have exhausted all existing data available from surrogates and other referenced data provided (see below) with the explanation to why this data is insufficient to support the weight of evidence approach for determination of hazard of the PMN substance and that new animal testing is the only option available to eliminate the risk concerns by the agency. We request a response to address each of the aspects of the references listed and we would find it helpful to have a follow-up call with you or Jeff Morris in attendance.
>
> 1. Analog 1 (provided in P2 Assessment) OECD 422/414 and 90 Day Repeat Dose; and additional Analog (provided in 03.24 email) OECD 414 Study (oral) C16-C18 Alkyl esters of the fatty acid of concern
>   a) Page 6 of updated Risk Assessment Summary received by fax 5/8/2018. Based on data provided on the average molecular weight fraction of the fatty acids, the risk assessor made new implied references determining that the analog would not be "closest fatty ester analog". However, analytical characterization data provided in the PMN clearly shows the % weight fraction of each of the prominent tetraesters present as constituents of the PMN substance which actually includes the analog.

- It is our position that Analog (1) is not only a constituent, it carries the highest concentration of the fatty acid of concern potentially available giving best worst case concentration and provided additional references in my 03/24/2018 email that were not addressed by the risk assessors. Based on the additional references we provided, there is not expected to be a difference in the rate of enzymatic hydrolysis of the branched tetraesters and the combination linear and branched tetraesters. The rate of hydrolysis is more dependent on the esterification and all species substituted with greater than 3 ester groups were found to be 2000 times slower (Mattson and Volpenhein, 1972a, b).

b) The risk assessor makes an important statement regarding the metabolism of the tetraester by dermal absorption versus gastrointestinal: "Furthermore, dermal exposure would bypass the liver and gastrointestinal metabolism of the fatty acid esters increasing the uncertainty of oral studies based on the intact ("Analog 1") molecule. Thus, the oral developmental study in rats for ("Analog 1") was not utilized for regulatory decisions."
   - There still seems to be a contradiction on what testing we would do on the PMN substance based on the above. During our last conversations this week, we discussed an additional oral 422 on the PMN substance in order to extrapolate to inhalation and dermal. If the risk assessor has excluded analog data based on on oral ingestion, it is unclear why additional testing on PMN substance would be acceptable. See additional number 5) below regarding inhalation.
   - Alternatively, it is not clear why the tetraester data by oral ingestion is not sufficient to support a finding of "no concern", but developmental toxicity data from oral ingestion of the fatty acid is acceptable to use in calculations to determine there is a concern.
   - If the risk assessor does believe that the dermal exposure would bypass the liver and gastrointenstinal metabolism of the fatty acid esters, it is not clear why there is still concern for developmental toxicity. See number 2) below for additional reference material provided regarding the importance of the concentration of the fatty acid reaching the liver.
   - After exhausting all public searches, every study found that was conducted on a polyol or alkyl esters in connection with the developmental toxicity of the fatty acid of concern was based on oral ingestion. No new dermal exposure studies could be found, even when chemicals were specifically tested recently due to use in cosmetics for dermal leave-on applications. Reasoning provided for the oral route chosen by the study directors for those studies was due to expected higher risk of concentration of the fatty acid metabolites from esterase in the gastrointestinal tract over any other routes. Oral ingestion would give the best representation of the worst case potential for systematic and developmental toxicity concerns subsequently ruling out the need for additional dermal or inhalation studies. It is our position that the 422 and 414 data provided representing both a tetraester and an alkyl ethylhexanoate provide best weight of evidence that the PMN substance is not expected to have systematic or developmental toxicity concerns.

2. Additional supporting references: CIR Safety Assessment of Alkyl Ethylhexanoates, 2012: http://www.cir-safety.org/sites/default/files/ethylh122012tent_faa_final%20for%20posting.pdf ; CIR Safety Assessment Pentaerythritol Tetraesters, 2012: https://www.cir-safety.org/sites/default/files/Pentae122011FINAL%20for%20posting.pdf

   a) *.."2-Ethylhexanoic acid has been shown to be a liver and developmental toxicant at high dose levels. In developmental studies, it has been postulated that 2-ethylhexanoic acid maternal liver toxicity begins a cascade of effects that includes metallothionein (MT) induction, zinc accumulation in the liver due to MT binding, and a resulting zinc deficiency in the developing embryo. In this model, it is the zinc deficiency in the developing embryo that causes developmental toxicity. Support for this mechanism of action comes from several sources. Animal studies have demonstrated that dietary zinc supplementation reduces the toxic effect and that further zinc deficiency makes 2-ethylhexanoic acid more toxic. In vitro studies using embryo cultures have demonstrated that either zinc deficiency or 2-ethylhexanoic acid treated sera produced developmental toxicity. Zinc supplementation of either/both sera eliminated the effect."*

b) Additional studies have been conducted to prove the hypothesis that the pathway to 2-ethylhexanoic acid production from a precursor would not give rise to acute liver toxicity, MT induction, zinc sequestration, and developmental toxicity. CIR safety panel concluded that the category of PE tetraesters were not likely to pass through the dermal layer as these ingredients have very poor solubility in water and have large molecular weights and additionally ethylhexanoates were precluded from risk of developmental toxicity from dermal exposure due to metabolic conversion that results in a time course of 2-ethylhexanoic acid appearance that allows clearance before sufficient levels can arise to produce acute liver toxicity.

c) Risk assessor does make reference to the Canadian Draft Screening Assessment of Ethylhexyl Ethylhexanoate from 2017 which also relied on risk calculations using the same oral developmental toxicity data available for the fatty acid as EPA, but also summarize that their calculations are assuming .."to the extent hydrolysis is unknown, it is conservatively assumed that all of 2ethylhexyl 2-ethylhexanoate is hydrolyzed to 2-EHA, followed by complete absorption through the skin (i.e., assuming that absorption through the dermal route is equivalent to absorption through the oral route").. The Canadian reference did not consider available data from additional alkyl ethylhexanoates such as what was provided to EPA and did not include the comments or new data received after the draft was published in 2017. The Final Assessment from Canada was expected to be published after March 2018 but could not be found as of yet.
    - The OECD 414 study referenced for the additional Analog listed in number 1) above supports the hypothesis and conclusions made by the CIR Safety Assessment.
    - If the risk assessor agrees the dermal exposure would bypass the liver and gastrointenstinal metabolism of the fatty acid esters, it is not clear why there is still concern for developmental toxicity.

3. Analog 2 (provided in P2 Assessment) and the EPA High Production Volume Assessment of Polyol Esters Category, 2010 (see attached)
    - Page 8 of updated Risk Assessment Summary received by fax 5/8/2018. We have provided our concerns about the study referenced has a LOEL of 2000 mg/kg/day (NOAEL of 800 mg/kg/day) and is included in the 2010 HPV Screening Assessment for Polyol Esters Category of chemicals. This study has been used by EPA as a basis of risk determination for the Polyol Esters Category in the past "as not likely" for human health concerns. Based on that study, EPA made the determination in 2010 that no further testing was necessary for the category, however, the use in the risk calculation would seem to be a reversal of EPA's earlier findings for HPV chemical category, is this the case? Since 2010, there have been multiple subsequent 90-day repeat tox and OECD 421/422/414 oral reference data generated for the Polyol Esters Category that has contributed to the weight of evidence for the category that these chemicals are of low concern.
        - Specifically, are you in an agreement that based on data provided in the 2010 HPV Assessment, the chemical category is lacking data for dermal exposure to address concerns summarized by the risk assessor? Has this been applied consistently previously and will apply similar to future submissions under the polyol ester category?

Additional Notes:

4. Page 1 of the updated risk assessment summary provided to us in fax 05/8/2018 indicated that risk were not identified for worker for inhalation because exposure is negligible, however, the PM continues to insist there will be a proposed SNUR to address risk from inhalation due to spray applications. To our knowledge, beyond our applications, the only potential industrial uses (not including FDA regulated uses) identified of polyol tetraesters from public resources have been for lubricating oils of jet engines, low-temperature use grease, heat-resistant engine oil, and refrigerator oil which have not indicated any foreseeable use including spray applications. From discussions regarding testing, we do have a concern that there will be adjustments in the recommended testing to eliminate the proposed SNURs that would also address inhalation even though no concerns were indicated by the risk assessor or before any additional modeling/calculations indicated concern.

5. Page 8 of the updated risk assessment summary provided to us in fax 05/8/2018, there is still an error in the risk calculations after amendment by the risk assessor based on data cited from our PMN or P2 assessment. It does not greatly affect the outcome, but should still be noted for accuracy or if the results are further used in additional determinations. The "worst case" exposure from the handling of filter

media from the manufacturing process should still have a concentration adjustment of 50% wt/wt of the PMN chemical in the solid and when combined with the adjustment for the % fatty acid would result in a 14.3% Structural Alert/Component as % PMN Substance.

6. Page 9 of the updated risk assessment summary provided to us in fax 05/8/2018, the risk assessor has made reference to Cargill Technical documents and a study found online which apply to Cargill's Natural Esters used in the same use applications. The Natural Esters referenced in this application are primarily vegetable oils with additives which are a different category of chemicals. Synthetic Esters are designed to have better stability to extreme temperature variations when compared to our Natural Esters and do not use the same Technical Guidance for handling and storage. The following was provided by my technical team for additional information for consideration:
    - It is not anticipated that transformers are opened, even for maintenance, for the life of the transformer (20-60 years)
    - For some transformers (such as switch gears), any sampling or contact with the fluid is uncommon; there would be 40-60 years without exposure to oil
    - Where there are routine assessments in place, the sampling of the oil is done in a very controlled manner ranging from a 6 month to bi-annual basis. Amounts ranging from 50 ml to 1 L samples are taken with a syringe, taking great care to keep the transformer oil sealed from air or exposure – often through some type lock and bleed valve
    - One of the standards tested from this analysis is Acid Value, which dictates an upper acidity limit of the oil to be below 0.3 mg/g KOH – the fluid is expected to remain well below this level for the life of the transformer (40-60 years).
    - Other maintenance or contact with the fluid is not expected for the life of the transformer
    - Additionally, per the IEEE standard C57.154 (we can provide) – the max allowable temperature of operation for a transformer (and only for a short time in emergency conditions) is 140 C. This is recognized by UL, a well-known industry standard, which the industry adheres to.

Thanks again for your diligence with your teams and support to get to a good resolution. As I provided previously, we may want an additional call or meeting which would include either yourself or Jeff so that we can expedite the next steps forward and if that will include additional 422 testing on our part.

Best regards,

Anastasia

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From: Beck, Nancy <Beck.Nancy@epa.gov>
Sent: Friday, May 11, 2018 5:01 PM
To: Anastasia Coots <Anastasia_Coots@cargill.com>; Bauer, Jeff <Bauer.Jeff@epa.gov>; Morris, Jeff <Morris.Jeff@epa.gov>
Cc: Robin Eichen-conn <Robin_Eichen-Conn@cargill.com>; Hanley, Mary <Hanley.Mary@epa.gov>; Bolen, Derrick <bolen.derrick@epa.gov>
Subject: RE: Request Suspend P-18-0101 for further review

Hi Anastasia,
I've heard you've now had a few calls with the program and hopefully we are moving towards a common understanding and good resolution.
Please let me know if you have further concerns.

Regards,
Nancy

Nancy B. Beck, Ph.D., DABT
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From: Anastasia Coots [mailto:Anastasia_Coots@cargill.com]
Sent: Wednesday, April 25, 2018 4:40 PM
To: Bauer, Jeff <Bauer.Jeff@epa.gov>; Morris, Jeff <Morris.Jeff@epa.gov>; Beck, Nancy <Beck.Nancy@epa.gov>
Cc: Robin Eichen-conn <Robin_Eichen-Conn@cargill.com>
Subject: Request Suspend P-18-0101 for further review

Hello Jeff,

We will need to suspend the PMN for at least 15 days as we discussed in order to give us time to respond to the most recent information received from the risk assessment team. I will be out of office until May 7th but can still be reached by cell phone.

I received the fax of the risk assessors summary based on the changes to calculations and the addition of other data or endpoints since reviewing with Nancy more than three weeks ago. I did actually expect the reports or summary presented to Nancy to be included and the explanation to the changes. I had also expected some summary or additional detail on their determinations to why the assessors chose not to use the additional OECD 421/422, repeat tox data, and referenced material that we have provided for analogs of the ester. Will it be possible to get the additional determinations in writing for the reference data provided and why they are still choosing the LOEL for the fatty acid and not any of the toxicity data provided on the substantially similar esters?

For us, this is not about not wanting to require gloves through a SNUR. This is about the potential commercial impact of the additional regulatory burdens of a SNUR and the perceived health risk implied to this chemical versus others used in industry.

We need better guidance on what data and scientific evidence or references that can be provided that will elevate the concerns raised by the risk assessors. From our conversation, the indication that even if we did complete new OECD 421/422 with a positive outcome of a NOAEL of 1000 mg/kg/day or greater using our manufactured chemical would not change the risk assessors concerns that are driving the recommendation for a SNUR is insufficient for us to be able to address how to move forward.

We will make a full response or would like to provide additional information if possible for review but also need better understanding of the additional references newly added by the risk assessor to support their concerns.

The second point of the summary, references a repeat tox dermal absorption study that was used as a secondary NOAEL for risk calculations by the assessors to support concerns. The study referenced has a LOEL of 2000 mg/kg/day (NOAEL of 800 mg/kg/day) and is included in the 2010 HPV Screening Assessment for the category of chemicals. This study has been used by EPA as a basis of risk determination for the chemical Category in the past "as not likely" for human health concerns. Based on that study, EPA made determination in 2010 that no further testing was necessary, however, the use in the risk calculation would seem to be a reversal of EPA's earlier findings for HPV chemical category. Is

EPA reversing their previous determinations for the whole category under the HPV Assessment? There has been multiple subsequent 90-day repeat tox and OECD 421/422/414 oral reference data submitted that has been used as a weight of evidence for the category. It is unclear why it would now be used in risk calculations to support concerns?

We would like to also provide additional supporting information or data in regards to the third and last claims of the potential thermal degradation of the chemical made by the risk assessor in their summary, however, they did not provide any references to what they are basing their assumptions. Our knowledge and the additional industry standards which require testing under ISO, IEEE, UL certifications do not support the statements made by the risk assessors. We would like guidance on what information they are using as reference or data that we can provide that would be helpful to review to elevate this concern.

Thanks,

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